Clinical review

Human African trypanosomiasis

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The re-emergence of sleeping sickness presents a major public health problem

Human African trypanosomiasis or sleeping sickness is one of the most important but equally most neglected tropical infections. It is caused by a protozoan, *Trypanosoma brucei*, which is transmitted to humans through the bite of a tsetse fly (*Glossina* spp).[1] Patchy distribution of the various vector species confines the disease to some 200 microfoci in sub-Saharan Africa (fig 1). The disease had been successfully controlled by a combination of approaches, including treatment of patients, active case finding, and measures to deal with the vector.[2] Since the 1970s, however, the disease has re-emerged as a new epidemic of immense proportions, which, until recently, received little attention from the international community (fig 2). According to the World Health Organization, about 500 000 people already carry trypanosomes and will die if left untreated.[3]

Summary points

- Human African trypanosomiasis is a re-emerging public health problem of epidemic proportions in many parts of rural Africa
- The disease is caused by subspecies of *Trypanosoma brucei* and is transmitted by tsetse flies
- Treatment requires admission to hospital and is costly, potentially dangerous, and limited by the widespread appearance of drug resistances
- Investment in clinical and pathophysiological research and a broad international commitment to fight trypanosomiasis in Africa are urgently needed

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Sources and methods

Extensive literature exists on human African trypanosomiasis and trypanosomes, but it is mostly confined to basic sciences and neglects clinical research and the impact of the disease on large parts of the population in rural Africa. One of the countries most affected is Angola. In the north, local health professionals are involved in a control programme implemented through the Catholic charity, Caritas. Some 14 000 patients have already been treated and more than 100 000 examined for the disease within the past five years. Our review is based on our experiences from this project as well as from molecular and parasitological studies of the trypanosome itself.

Epidemiology

Human African trypanosomiasis exists in two forms with different clinical presentations and epidemiology caused by morphologically indistinguishable subspecies of *T brucei* (fig 3). The trypanosome is transmitted by different species of tsetse flies, which have differing predilections for breeding sites. West African sleeping sickness, caused by *T brucei gambiense*, has always been a continuous, but is now a re-emerging, threat to some 60 million people in west and central Africa as well as some parts of east Africa (fig 1).

East African sleeping sickness, caused by *T brucei rhodesiense*, is a zoonosis with an extensive animal reservoir in ungulates, including game animals. Animal trypanosomiasis (Nagana disease) is a serious obstacle to the introduction of livestock not sufficiently adapted to this disease and is therefore of great economic consequence. Cattle infected with trypanosomes become chronically ill, are lost for milk and meat production, and eventually die of prostration and intercurrent infections. Sporadic human cases may occur in areas where people intrude into tsetse infested habitats of animal reservoirs, and there can be a risk of larger outbreaks if whole populations are driven "into the bush" as a result of civil unrest.[4] A recently reported cluster of

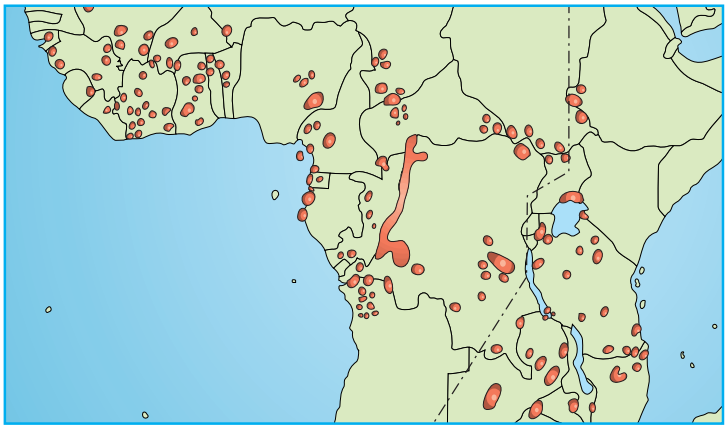

Fig 1 Distribution of human African trypanosomiasis in sub-Saharan Africa

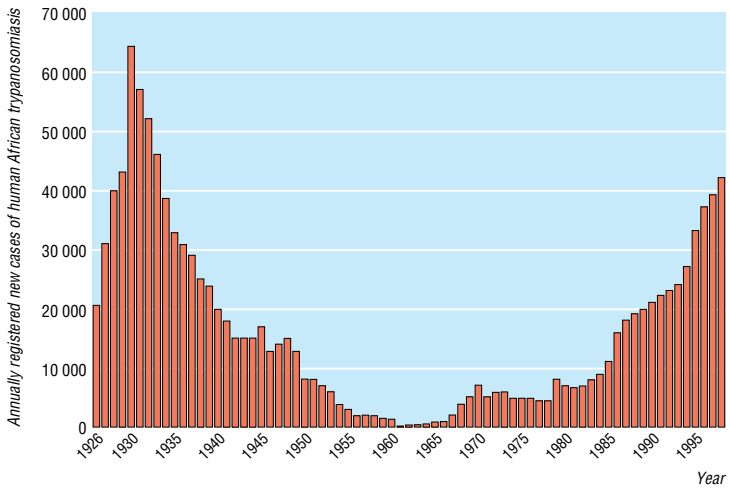

Fig 2 Number of newly registered cases of human African trypanosomiasis in past 75 years according to WHO

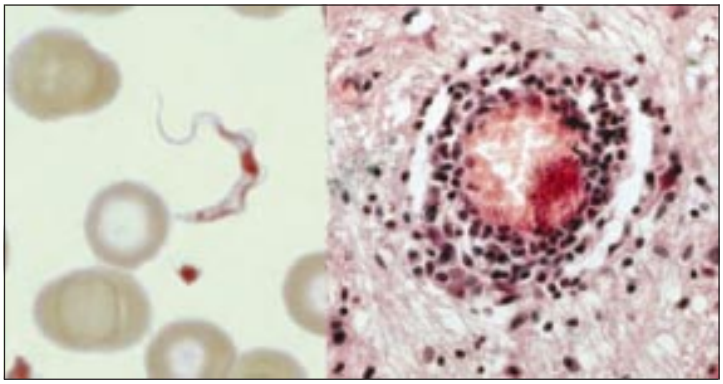

Fig 3 Left, *Trypanosoma brucei* in blood (Giemsa × 1000). Right, typical pathohistological changes (perivascular cuffing) in a brain section of patient with sleeping sickness (haematoxylin and eosin × 400)

human African trypanosomiasis among European tourists visiting national parks in northern Tanzania brought this zoonosis to the attention of the medical community in the West, highlighting its importance not only as a plague for people in endemic areas but also as a threat to travellers in rural Africa.[5] The disease must therefore also be considered in the differential diagnosis of fever in patients returning from many African countries.

Clinical presentation

Local symptoms

Human African trypanosomiasis is a disease that evolves through clinically distinct stages, with a lethal outcome if left untreated.[6] The first symptoms begin at the site of the tsetse fly's bite after a minimum of five days. This local skin reaction is called a trypanosomal chancre. It is typically accompanied by regional lymphadenopathy and is more common in east African trypanosomiasis than in west African trypanosomiasis.

First stage of disease

As the disease progresses from local symptoms to the first stage of a generalised infection, fever is one of the commonest, albeit non-specific, signs. Usually the pattern of fever is irregular over many weeks, reflecting progressive waves of parasites multiplying in the blood. In east African trypanosomiasis, symptoms at this stage of infection can already be severe: around one tenth of patients without rapid access to treatment will die, often due to myocardial involvement. Early symptoms in west African trypanosomiasis are usually more inconspicuous. Lymphadenopathy, especially in the posterior triangle of the neck (Winterbottom's sign), is characteristic. Hepatosplenomegaly and a faint rash are other common non-specific signs.

Second stage of disease

In the second stage of the disease, beginning after weeks in east African trypanosomiasis and months in the west African form, trypanosomes cross the blood-brain barrier by unknown mechanisms and invade the central nervous system.[7] This second stage results in a chronic encephalopathy (fig 3), associated with headache and mental changes. Patients have reduced higher mental functions, difficulty in concentration, are increasingly unable to cope with their surroundings, and eventually enter a terminal somnolent state, which gives the disease its name in many languages: sleeping sickness, maladie de sommeil, doença do sono (fig 4).

Difficulties in diagnosis

The diagnosis of human African trypanosomiasis requires a high degree of training and expertise. Initially, the parasite must be detected. This relies on conventional techniques such as lymph node puncture, blood film examination, or various more elaborate techniques to concentrate parasites in the blood.[8] As the concentration of trypanosomes in the blood undulates, often decreasing below detection levels in west African trypanosomiasis, examinations may have to be repeated daily.

Molecular or serological tools have not replaced these classic parasitological procedures. For conditions in the field the card agglutination test for trypanosomiasis is a useful complementary screening tool in west African trypanosomiasis.[9]

Once trypanosomes have been detected in blood or lymph the disease needs staging by lumbar puncture. Increased lymphocyte counts ($\geq$20 cells/µl), increased protein levels ($>$35 mg/dl), or the presence of trypanosomes in cerebrospinal fluid confirms the involvement of the central nervous system. This differentiates between stage 1 (haemolymphatic stage) and stage 2 (encephalitic stage), essential for the correct choice of treatment.

Treatment

The range of drugs that are used against human African trypanosomiasis is limited (box 1). Only one of them is less than 40 years old. Until recently melarsoprol, a compound containing arsenic, was the only treatment readily available for stage 2 disease, but it is associated with 4% to 12% mortality.[10] Its main adverse effect is an acute encephalopathy, occurring around 8 to 10 days of treatment. For adjunctive therapies, only prednisolone for stage 2 disease is supported by sufficient clinical evidence.[11] Treatment lasts a minimum of 10 days and, at least for stage 2, requires

Box 1: Drugs used to treat human African trypanosomiasis

West African trypanosomiasis
Stage I
First line: pentamidine
Second line: eflornithine or melarsoprol

Stage 2
First line: melarsoprol
Second line: eflornithine

East African trypanosomiasis
Stage 1
First line: suramin
Second line: melarsoprol

Stage 2
First line: melarsoprol
Second line: nifurtimox combined with melarsoprol

admission to hospital, specialist nursing care, and intensive monitoring.[12]

Until the start of 2001 the treatment of patients with sleeping sickness was at risk. The pharmaceutical industry stopped producing most antitrypanosomal drugs as their sale generated insufficient profit. An acute shortage emerged, with growing fear that soon no drugs would be available to treat stage 2 disease. At the same time new production lines for cosmetics were opened for the North American market with eflornithine, an antitrypanosomal drug, being used in depilatory creams. Health organisations protested against this, and the media blamed the pharmaceutical industry for not facing up to its humanitarian responsibilities. An agreement was finally reached between Aventis (press Release, 3 May 2001) and Bayer, the WHO, and Médécins sans Frontières. Aventis and Bayer assure free production of the five essential antitrypanosomal drugs (see box) for the next five years, the WHO will coordinate their distribution in Africa, and Médécins sans Frontières will take over storage and shipment. This example of public-private partnership has been important in the struggle against sleeping sickness.

The availability of antitrypanosomal drugs, however, helps to solve only one part of the enormous problem of the re-emerging crisis in Africa. Medical teams in the field need better drugs and improved treatment schedules as they still face an unacceptably high treatment related mortality as well as increasing resistance from the parasite.[13] Control of the disease needs a firm and sustainable commitment of political institutions, healthcare providers, and donor agencies over a long time, and a stable socioeconomic environment. War, civil unrest, corruption, and economic decline are the grim reality in many endemic areas, making the battle against human African trypanosomiasis still look lost.

Ongoing research

Most research in trypanosomiasis over the past 30 years has focused on molecular and biochemical aspects of the trypanosome. As animal trypanosomes are easy to maintain in culture and multiply rapidly, they have evolved to become the models of researchers in the field of molecular parasitology and immunology. Many important phenomena such as antigenic variation, eukaryotic polycistronic transcription, and RNA editing have first been described in the trypanosome model.[14 15] Apart from these achievements, the research community in the 1980s and '90s took little interest in trying to understand the clinical aspects of infection and its management. Apart from a few noteworthy exceptions, work on the pathophysiological background of the disease or properly conducted clinical trials did not take place.[16] The gap between basic and clinical research, well known for many tropical diseases, is therefore widest in human African trypanosomiasis.

But this situation is changing. Current work is aimed at optimising the use of antitrypanosomal drugs, minimising their toxicity,[16] and developing new compounds. The growing problem of drug resistance to pentamidine and melarsoprol has driven clinicians to consider combination chemotherapy regimens. The high mortality of patients treated with stage 2 disease also suggests that studies to examine the general pathophysiology of infection, including treatment induced encephalopathy, may lead to completely new management regimens and adjunctive therapies.

Logistical issues, however, pose some major problems to research. The sites where human African trypanosomiasis exists are notoriously difficult to access and are often located in areas of civil unrest. To establish a research environment in countries such as rural Angola or the Democratic Republic of Congo is a major challenge.

Perspectives for the future

A host of fundamental questions relating to human African trypanosomiasis needs to be answered

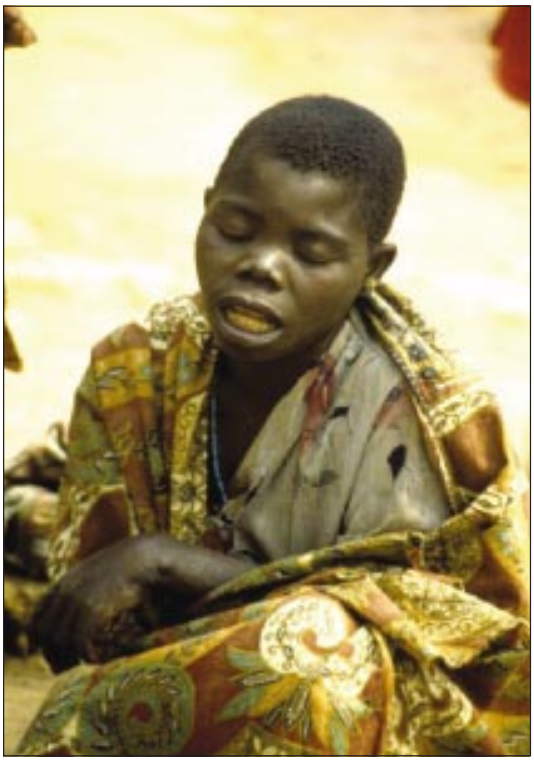

Fig 4 Angolan woman with terminal stage of sleeping sickness

Box 2: Some fundamental unanswered questions in human African trypanosomiasis

How do trypanosomes enter the nervous system?

How does the infection kill?

How can recent findings on mechanisms of drug resistance that have been identified in laboratory models be translated into useful tools in the management of affected patients?

How should targets be selected from biochemical studies against which new drugs can be designed?[17]

How can efforts to fight the disease in Africa be effectively combined on a local, national, and international level?

urgently (box 2). The investment in clinical and applied aspects of research into the disease is so dire that even small amounts of additional funding are likely to produce disproportionately large returns. Sustained donor commitment to clinical and applied aspects of the disease will also play a critical part in providing novel treatments that are effective and substantially free of side effects, that can be given orally, and that are affordable at the point of use.

Sleeping sickness can be controlled. Even with the limited tools available 50 years ago, it was possible to eliminate the disease as a public health problem in most areas of Africa. Today we are facing a new epidemic that we can fight with an even better repertoire of measures if there is political will and a sustained commitment of all decision makers.

Competing interests: None declared.

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Additional educational resources

Useful books

Molyneux DH, Pentreath V, Doua F. African trypanosomiasis in man. In: Cook GC, ed. *Manson's tropical diseases*, 20th ed. Philadelphia: WB Saunders, 1996.

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World Health Organization. *Control and surveillance of African trypanosomiasis*. Geneva: WHO, 1998. [WHO Technical Report Series 881.]

Useful websites

World Health Organization (http://www.who.int/emc/diseases/tryp/)—information on programme for surveillance and control of African trypanosomiasis (http://www.who.int/inf-fs/en/fact259.html)—fact sheet detailing most aspects of African trypanosomiasis

Centers for Disease Control and Prevention (http://www.cdc.gov/ncidod/dpd/parasites/trypanosomiasis/default.htm)—fact sheets and professional information from the Division of Parasitic Diseases

Food and Agriculture Organization of the United Nations (http://www.fao.org/paat/html/home.htm)—description of the programme against African trypanosomiasis information system

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One hundred years ago

Two remarkable medical women

MADAME ROSALION-SOCHALSKAIA, who died lately at Poltawa, in Russia, was a somewhat remarkable type of the medical woman. Having won a considerable reputation in the literary world as a writer of children's books and as a translator, she began the study of medicine at the age of 54, at the same time as her daughter. After finishing her medical studies she practised her profession with success while continuing to write for the press. She was physician to a high school for girls at Poltawa, and teacher of massage in the Upper School of *Feldschers*, or trained surgical assistants. The *Lyon Médical* gives some particulars as to another Russian lady who also began the study of medicine when she was over 50. She had cherished the desire to study it ever since she had lost a child from diphtheria. She wished to devote herself specially to research on that disease with the object of finding a remedy. Hardly, however, had she finished her studies when Behring's discovery of the diphtheria antitoxin was announced. We gather that the lady, being satisfied that the object of her proposed research had been anticipated, gave herself to the work of general practice.

(*BMJ* 1902;ii:202)